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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.		
10/770,668	02/02/2004	Susan C. Wright	115-000420US	2158		
	7590 04/09/200 LECTUAL PROPERT	EXAMINER				
P O BOX 458		FETTEROLF, BRANDON J				
ALAMEDA, C.	A 94501	ART UNIT	PAPER NUMBER			
		1642				
SHORTENED STATUTOR	Y PERIOD OF RESPONSE	. MAIL DATE	DELIVER	DELIVERY MODE		
3 MONTHS 04/09/2007			PAPER			

## Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summer		Application	Application No. Applicant(s)		-				
		10/770,668	•	WRIGHT ET AL.					
Office Action Summary			Examiner		Art Unit				
				Fetteroif, PhD	1642				
Period fo	The MAILING DATE of this communic or Reply	cation appe	ears on the (	cover sheet with the c	orrespondence ad	dress			
WHIC - Exter after - If NO - Failu Any	ORTENED STATUTORY PERIOD FO CHEVER IS LONGER, FROM THE MA issions of time may be available under the provisions of SIX (6) MONTHS from the mailing date of this commu- period for reply is specified above, the maximum state to reply within the set or extended period for reply very reply received by the Office later than three months afted patent term adjustment. See 37 CFR 1.704(b).	AILING DA of 37 CFR 1.136 unication. tutory period wi vill, by statute, o	ATE OF THIS 66(a). In no even ill apply and will ocause the applic	S COMMUNICATION t, however, may a reply be time expire SIX (6) MONTHS from ation to become ABANDONE	l. lely filed the mailing date of this co D (35 U.S.C. § 133).				
Status									
1)	Responsive to communication(s) filed	d on <u>16 Ja</u>	nuary 2007.						
	This action is <b>FINAL</b> . 2b)⊠ This action is non-final.								
3)	Since this application is in condition f	or allowan	ice except fo	or formal matters, pro	secution as to the	e merits is			
	closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.								
Dispositi	on of Claims								
4)🖂	Claim(s) 1-19 is/are pending in the ap	oplication.							
	4a) Of the above claim(s) is/are withdrawn from consideration.								
5)	5) Claim(s) is/are allowed.								
6)⊠	6)⊠ Claim(s) <u>1-19</u> is/are rejected.								
7)	Claim(s) is/are objected to.								
8)□	Claim(s) are subject to restrict	ion and/or	election red	quirement.					
Applicati	on Papers								
9)	The specification is objected to by the	Examiner	r.						
10)	The drawing(s) filed on is/are:	a) acce	epted or b)	objected to by the E	Examiner.				
	Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).								
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).									
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.									
Priority ι	ınder 35 U.S.C. § 119								
12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of:									
	1. Certified copies of the priority documents have been received.								
	2. Certified copies of the priority documents have been received in Application No								
	3. Copies of the certified copies of the priority documents have been received in this National Stage								
	application from the International Bureau (PCT Rule 17.2(a)).								
* See the attached detailed Office action for a list of the certified copies not received.									
A44-a4									
Attachment(s)  1) Notice of References Cited (PTO-892)  4) Interview Summary (PTO-413)									
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) Paper No(s)/Mail Date									
	nation Disclosure Statement(s) (PTO/SB/08) r No(s)/Mail Date 9/20/2006.			5) Notice of Informal P 5) Other:	atent Application	·			

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### Response to the Amendment

The Amendment filed on 1/16/2007 in response to the previous Non-Final Office Action (7/12/2006) is acknowledged and has been entered.

Claims 1-19 are currently pending and under consideration.

#### Information Disclosure Statement

The Information Disclosure Statement filed on 9/20/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

#### Rejections Withdrawn:

The rejection of Claims 1-2 under 35 U.S.C. 102(b) as being anticipated by Bandman et al. (US 6,274,138, 2001) has been withdrawn in view of Applicants arguments.

#### New Rejections upon Reconsideration:

### Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

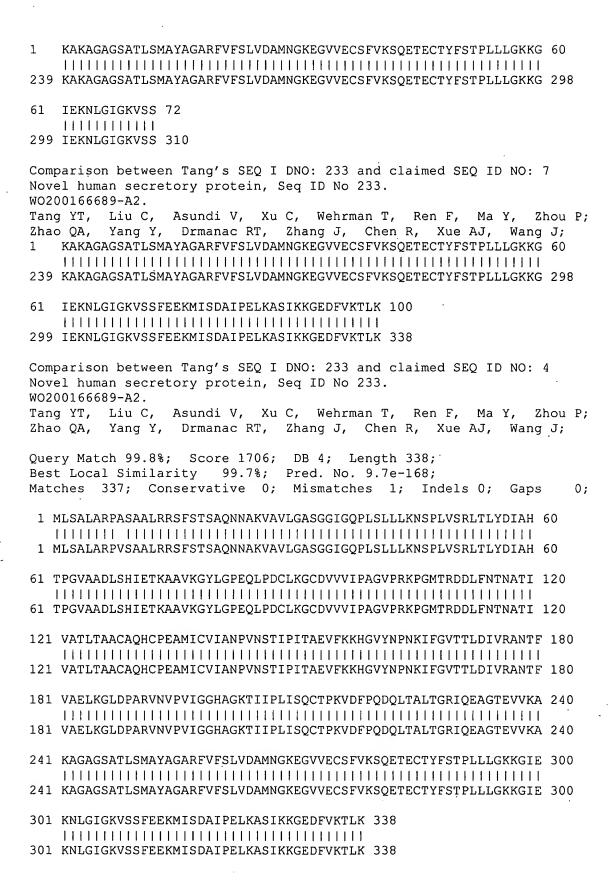
Claims 1-5, 8 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (WO 01/66689 A2, 2001, of record).

Tang et al. teach a composition comprising an isolated amino acid sequence, which has at least 99.8% sequence identity to the claimed SEQ ID NO: 4, comprising the instantly claimed amino acid sequence of SEQ ID NO: 6 and/or 7 and having SEQ ID NO: 4 (SEQ ID NO: 233 of WO publication, see below sequence comparison). With respect to the amino acid sequence, the WO publication teaches that the amino acids include, but are not

limited to, both full length (comprising a signal sequence) and mature forms (without a signal sequence) (page 28, lines 19-20). Moreover, Tang et al. teach that the polypeptides may be operably linked to a targeting moiety such as an antibody which binds to a cell molecule (page 32, lines 1-14 and line 34 to page 33, line 25). For example, the WO publication teaches that the polypeptides may be operably linked to an antibody which specifically binds a target on pancreatic cells. In the instant case, the transitional phrase "comprises", which is synonymous with "including," "containing," or "characterized by," recited in the current claims is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising," the terms containing' and mixture' are open-ended."). < Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.). Thus, in view of the transitional phrase, Tang et al. teach a composition comprising a portion of SEQ ID NO: 4, wherein the portion comprises SEQ ID NO: 6 or SEQ ID NO: 7. Moreover, although Tang et al. does not specifically teach that the polypeptide has activity chosen from DNA nuclease activity and cell killing activity, the claims are drawn to the product per se and inherently, such a polypeptide have activity chosen from DNA nuclease activity and cell killing activity. Thus, the claimed peptide appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Comparison between Tang's SEQ I DNO: 233 and claimed SEQ ID NO: 6 Novel human secretory protein, Seq ID No 233. WO200166689-A2.

Tang YT, Liu C, Asundi V, Xu C, Wehrman T, Ren F, Ma Y, Zhou P; Zhao QA, Yang Y, Drmanac RT, Zhang J, Chen R, Xue AJ, Wang J;



Note: In order to Expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection under 102(b) as being anticipated by Tang. As a preliminary matter, Applicants assert that only page 1 of Tang et al. was provided to Applicants; and further, after reviewing Tang et al. on line, it appears that no sequences are provided in the published reference, making the relevance of Tang et al. rather unclear. Applicants further submit that certain of the priority documents of Tang et al. include over 600 hundred pages worth of sequence listings. Thus, Applicants take the Examiner's argument to be that one of these many thousands of sequences (see also Tang et al. claim 1) includes an MDH sequence that is the same as SEQ ID NO: 4 of the subject application. Assuming, arguendo, that the Actions statements regarding the presence of an MDH sequence in Tang are correct, Applicants argue that the reference still completely fails to disclose a polypeptide wit the claimed activity. For example, Applicants assert that the Action argues that Tang teaches a mature form of MDH coupled to various targeting moieties. However, Applicants argue that the full length mature MDH does not have nuclease activation properties or cell killing activity and no fragment of MDH that possess these properties are taught by Tang or alleged in this action. As such, Applicants assert that the references, therefore, completely fails to meet the limitations in the claims.

These arguments have been carefully considered, but are not found persuasive.

Regarding the preliminary matter submitted by Applicants, the Examiner apologizes that only page 1 of Tang et al was provided to Applicants and believes that this may have been a problem with the mailing department at the office because it appears that Tang et al. was scanned into the system. With regards to the publication of the sequences, the Examiner acknowledges that the sequences were not published along with publication of WO 01/66689. However, the Examiner recognizes that the sequence listing part of the description was published separately in election form and was made available to the public upon request the International Bureau (see page 1, 2<sup>nd</sup> column, Published: of the WO publication). As such, Tang et al. meets the requirements of 35 U.S.C. 102(b) and is therefore relevant. Moreover, the Examiner has attached an amino acid sequence comparison between the claimed SEQ ID NO: 4 and Tang et al. SEQ ID NO: 233 which reveals that Tang et al.'s SEQ ID NO: 233 has 99.8% sequence identity to SEQ ID NO: 4.

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As such, Applicants arguments pertaining to Tang et al.'s peptide not having cell killing activity because SEQ ID NO: 4 simply does not have this activity are moot. As stated above, although Tang et al. does not specifically teach that the polypeptide has activity chosen from DNA nuclease activity and cell killing activity, the claims are drawn to the product *per se* and inherently, such a polypeptide comprising SEQ ID NO: 6 or 7 as claimed would have this functional limitation. Thus, the claimed peptide appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

#### Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

- 1. Determining the scope and contents of the prior art.
- 2. Ascertaining the differences between the prior art and the claims at issue.
- 3. Resolving the level of ordinary skill in the pertinent art.
- 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (WO 01/66689, 2001, of record) in view of Wang et al. (Cancer Research 1991; 51: 3353-3355, of record).

Tang et al. teach, as applied to claims 1-5, 8 and 17 above, a composition comprising an isolated amino acid sequence, which has at least 99.8% sequence identity to the claimed SEQ ID NO: 4, comprising the instantly claimed amino acid sequence of SEQ ID NO: 6 and/or 7 and having SEQ ID NO: 4 (SEQ ID NO: 233 of WO publication, see below sequence comparison). With respect to the amino acid sequence, the WO publication teaches that the amino acids include, but are not limited to, both full length (comprising a signal sequence) and mature forms (without a signal sequence) (page 28, lines 19-20). Moreover, Tang et al. teach that the polypeptides may be operably linked to a targeting moiety such as an antibody which binds to a cell molecule, wherein the targeting moiety increases the biological activity of the polypeptide (page 32, lines 1-14 and line 34 to page 33, line 25). In addition, the WO document teaches that the polypeptide is useful for the treatment of cancers including, but not limited to, liver cancer (page 53, lines 5-29).

Tang et al. do not explicitly teach that the antibody binds to liver cancer cells, wherein the antibody is Hepama-1.

Wang et al. teach a Hepama-1 antibody toxin conjugate. Specifically, the reference teaches that the hepatoma cytotoxicity of the conjugate was 500-fold higher as compared to the free toxin.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was to combine the teachings of the references so as to attach the polypeptide as taught by Tang et al. with an antibody such as Hepama-1 in view of the Wang et al. One would have been motivated to do so because Wang et al. teaches that the hepatoma cytotoxicity of the conjugate was 500-fold higher as compared to the free toxin. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by attaching the polypeptide as taught by Tang et al. with an antibody such as Hepama-1 in view of the Wang et al, one would achieve a method for specific delivery and targeting of the polypeptide for the treatment of liver cancer.

Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (WO 01/66689, 2001) in view of Wang et al. (Cancer Research 1991; 51: 3353-3355). In response to this previous rejection, Applicants assert that nothing in the

combination of references teaches the basic limitations of the claims. For example, Applicants assert that Tang et al. teach the mature MDH polypeptide which does not have DNA fragmentation/cell-killing acticity and Wang teaches nothing regarding an MDH polypeptide or fragment thereof. Moreover, Applicants assert that Tang et al. does not teach anything at all regarding anti-activity of any MDH polypeptide or fragment, but at best list several thousand nucleic acid and peptide sequences then alleges that some of the sequences "may" have any of a variety of activities listed on page 39-60 of Tang. However, Applicants assert that this is not a meaningful teaching to one of skill regarding any specific polypeptide activity for any specific polypeptide. Moreover, Applicants assert that it could just as easily be stated that somewhere in Genebank there may or may not be a gene that is involved with one or more medical disorders found in Harrison's guide to Internal Medicine. Yet, Applicants assert that this would not invalidate a latter invention that relies on the discover of a specific association between a gene and a disease, because, while the statement of Genebank might include some disease related genes is true it is meaningless in any practical sense.

These arguments have been carefully considered, but are not found persuasive.

Applicants arguments pertaining to Tang et al.'s peptide not having cell killing activity because SEQ ID NO: 4 simply does not have this activity have been discussed above and are incorporated herein. Regarding Applicants assertion that Tang et al. does not teach anything regarding the anticancer activity of any MDH polypeptide or fragment thereof, the Examiner acknowledges that Tang et al. does not explicitly teach the activity of any MDH polypeptide. However, the Examiner recognizes that Tang et al. clearly teaches that the polypeptides, including SEQ ID NO: 233, are useful for the treatment of cancers including, but not limited to, liver cancer (page 53, lines 5-29). As such, even if a reference discloses an inoperative device, it is prior art for all that it teaches. (emphasis added) Beckman Instruments v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Therefore, "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103." Symbol Techs. Inc. v. Opticon Inc., 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991).

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (WO 01/66689, 2001, of record) in view of Sherman et al. (2002/0022027, 2002, of record).

Tang et al. teach, as applied to claims 1-5, 8 and 17 above, a composition comprising an isolated amino acid sequence, which has at least 99.8% sequence identity to the claimed SEQ ID NO: 4, comprising the instantly claimed amino acid sequence of SEQ ID NO: 6 and/or 7 and having SEQ ID NO: 4 (SEQ ID NO: 233 of WO publication, see below sequence comparison). With respect to the amino acid sequence, the WO publication teaches that the amino acids include, but are not limited to, both full length (comprising a signal sequence) and mature forms (without a signal sequence) (page 28, lines 19-20). Moreover, Tang et al. teach that the polypeptides may be operably linked to a targeting moiety such as an antibody which binds to a cell molecule, wherein the targeting moiety increases the biological activity of the polypeptide (page 32, lines 1-14 and line 34 to page 33, line 25). In addition, the WO document teaches that the polypeptide is useful for the treatment of cancers including, but not limited to, liver cancer (page 53, lines 5-29).

Tang et al. do not explicitly teach that the polypeptide-antibody conjugate further comprises a cell internalization peptide and/or nuclear localization peptide.

Sherman et al. teach a composition comprising a Vpr polypeptide conjugated to a therapeutic molecule (ab). With regards to the Vpr peptide, the publication teaches that Vpr contains at least two nuclear localization signals and is capable of delivering molecules to the cell nucleus (page 1, 2<sup>nd</sup> column, paragraph 0006). With regards to the therapeutic molecule, Sherman et al. teach that the therapeutic molecules include, but are not limited to, polypeptides, polynucleotides and toxins (page 1, 1<sup>st</sup> column, paragraph 0007). Moreover, the publication teaches a method of killing a target cell and/or inhibiting cell proliferation or a target cell comprising administering a Vpr peptide conjugate or Vpr alone, wherein the Vpr conjugate is delivered into a cell and said cell is a cancer cell (abstract; page 1, 2<sup>nd</sup> column, paragraph 0008 and page 2, 1<sup>st</sup> column, paragraph 0010).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was to combine the teachings of the references so as to further attach a cell internalization/ nuclear localization peptide to the antibody-polypeptide conjugate as taught by Tang et al. in view of the Sherman et al.. One would have been motivated to do so because Sherman et al. teach that Vpr polypeptides conjugated to therapeutic molecules

allows for the selective delivery of the therapeutic molecule within the cell, wherein the therapeutic molecule is released from the Vpr by protease cleavage of the Vpr conjugate. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering an antibody-polypeptide conjugate as taught by Tang et al. in view of Wang et al. which further comprises a cell internalization/ nuclear localization peptide, one would achieve a method for specific delivery and targeting the polypeptide for the treatment of cancer.

Secondly, each of the agents, e.g., the polypeptide and a Vpr polypeptide, have been individually taught in the prior art as being useful for the treatment of cancer. As such, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Note: In order to Expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (WO 01/66689, 2001) in view of Sherman et al. (2002/0022027, 2002). In response to this previous rejection, Applicants that the rejections present similar issues to those which have been previously discussed above.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above.

#### Therefore, NO claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD Patent Examiner Art Unit 1642

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